DEVELOPMENT OF HEALTH CRITERIA FOR SCHOOL SITE RISK ASSESSMENT PURSUANT TO HEALTH AND SAFETY CODE SECTION 901(g):

Child-specific Reference Doses (chRDs) for Atrazine and Deltamethrin

DRAFT

Draft Report
December 2005

Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

DRAFT

DRAFT

LIST OF CONTRIBUTORS

Author
David Chan, D.Env.

Reviewers
David Siegel, Ph.D., DABT, Chief, Integrated Risk Assessment Branch
Jim Carlisle, DVM, Senior Toxicologist, Integrated Risk Assessment Branch
Robert Howd, Ph.D., Senior Toxicologist, Pesticide & Environmental Toxicology Branch
Lubow Jowa, Ph.D., Staff Toxicologist, Pesticide & Environmental Toxicology Branch
Robert Schlag, M. Sc., Res. Scientist III, Pesticide & Environmental Toxicology Branch
Jolanta Bankowska, Ph.D., Staff Toxicologist, Pesticide & Environmental Toxicology Branch
James Donald, Ph.D., Senior Toxicologist, Reproductive & Cancer Hazard Assessment Branch
Rajpal Tomar, Ph.D., Staff Toxicologist, Reproductive and Cancer Hazard Assessment Branch

Derek Gammon, Ph.D., Staff Toxicologist, California Department of Pesticide Regulation

George Alexeeff, Ph.D., Deputy Director for Scientific Affairs, OEHHA

Web-site Posting
Laurie Monserrat

DRAFT

Table of Contents

Introduction

Health and Safety Code (HSC), Section 901(g), requires the Office of Environmental Health Hazard Assessment (OEHHA), in consultation with the appropriate entities within the California Environmental Protection Agency, to identify those chemical contaminants commonly found at school sites and determined by OEHHA to be of greatest concern based on child-specific physiological sensitivities. HSC 901(g) also requires OEHHA to annually evaluate and publish, as appropriate, numerical health guidance values (HGVs) for five of those chemical contaminants until the contaminants identified have been exhausted. HGVs established by this mandate are intended for use in the assessment of risk at proposed or existing California school sites. At this time, OEHHA focuses its evaluation on non-cancer effects of the identified chemicals, pending the completion of a new method for developing HGVs based on child-specific carcinogenic effects. Accordingly, current HGVs are in the form of a child-specific reference dose (chRD) or child-specific reference concentration (chRC).

The Introduction serves as a background for the technical evaluation atrazine and deltamethrin. For those that are not familiar with this OEHHA program, it is advisable to review this chapter prior to analyzing the following technical reports.

Each technical chapter is a focused document that summarizes the chRD derivation. Recent reviews of the chemical by various entities, such as the U.S. Environmental Protection Agency (U.S. EPA), Agency for Toxic substances and Disease Registry (ATSDR), and California Department of Pesticide Regulation (CDPR), serve as a baseline for OEHHA to conduct additional literature search. In the document, OEHHA identifies relevant information from the baseline and from literature search for discussion. OEHHA will not reiterate basic data on environmental fate, pharmacokinetics, and pharmacodynamics that have been adequately covered in the cited baseline documents. Because these two technical chapters concern chRD derivations, non-cancer studies using an oral route of administration and studies that provide information regarding age-sensitivity are the primary focus of the OEHHA review. ChRDs will be applied for assessing health risk from oral or dermal exposure; whereas, chRCs derived from inhalation studies will be applied for assessing risk from inhalation exposure.

It should be underscored that a chemical-specific risk assessment is not required to support the development of chRDs. The purpose of establishing these child-specific health criteria is to provide improved means for consultants of school districts or the Department of Toxic Substances Control (DTSC) to conduct school site-specific risk assessment. The process here is similar to that used by U.S. EPA in developing reference doses (RfDs) for superfund site risk assessment. Thus, OEHHA is not considering exposure issues here. They will be dealt with in the site-specific risk assessment, specifically in the exposure assessment portion, which can be found in the "Guidance for Assessing Exposures and Health Risks at Existing and Proposed School Sites Pursuant to Health and Safety Code §901(f)," February 2004. The appropriate chRDs will be applied

only if site-specific sampling and analysis indicate the occurrence of the corresponding chemicals. The consultants will have the option to use, for example, default dermal or oral bioavailability factors provided in the exposure assessment guidelines, or proposed a departure from the default based on supporting data.

Developing a chRD or chRC

Challenge

The use of appropriate HGVs and exposure parameters is essential to provide an unbiased assessment of the health risk at an existing or a proposed school site. Since school children have higher air, food and water intake relative to their body weight compared to adults; and have activity or behavioral patterns that may lead to higher exposure to environmental contaminants than adults, these higher intakes and unique activity patterns need to be considered in developing a set of child-specific exposure parameters for use in the risk assessment. OEHHA has analyzed these exposure parameters in issuing the report, Guidance for Assessing Exposures and Health Risks at Existing and Proposed School Sites (http://www.oehha.ca.gov/public_info/public/kids/pdf/SchoolscreenFinal.pdf).

With respect to evaluating non-cancer risk by comparing the potential chemical exposure against the corresponding health criteria in the school setting, HGVs in the form of child-specific reference doses or concentrations should be used. Until the inception of the HSC 901(g) program, these child-specific HGVs were not available. For most part existing reference doses or concentrations for non-cancer endpoints, which were based on adult human or animal data, were used. The Food Quality Protection Act of 1996 (http://www.epa.gov/opppsps1/fqpa/) was an attempt to address the issue of children sensitivity. In addition to the traditional interspecies and intra-species uncertainty factors, it mandated a safety factor of 10 for the protection of children unless data existed to indicate that children were not more sensitive than adults. Thus, a question has been raised that the intra-species uncertainty factor of 10 would not adequately protect children because it was mainly designed to account for genetic variability such as metabolizing isoenzyme variations.

A case can be made for the development and application of child-specific HGVs based on studies in young animals or epidemiological analysis of pertinent data rather than relying solely on a safety factor or uncertainty factor. While locating the appropriate data are a challenge, OEHHA has strived to do so because children can be more (or less) susceptible to chemical effects due to pharmacodynamic and pharmacokinetic differences between them and adults, and thus empirical data in the young would be preferable. U.S. EPA and the March of Dimes sponsored a workshop -- Identifying Critical Windows of Exposure for Children's Health -- in September 1999 to systematically review the state of knowledge on prenatal and postnatal exposures and subsequent outcomes (Selevan *et al.* 2000). The workshop focused on the nervous, immune, respiratory, reproductive, and endocrine systems—organ systems that are still undergoing development and maturation in children and thus deemed to be highly vulnerable to chemical insults. Workshop participants noted that data pertaining to children's sensitivities to environmental

contaminants during various critical developmental periods are limited. In particular, little attention has been given to studying peripubertal/adolescent exposures or adult consequences from childhood exposure. Thus, the state of scientific knowledge pertaining to chemical effects on children is and will continue to be a limiting factor in OEHHA's ability to develop child-specific HGVs for these contaminants.

The evaluation of empirical data in the young can be a complex task. Vulnerability of the young often depends on the organ system in question and its developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, including adolescence. During its critical period(s), a particular structure or function is most sensitive to disruption due to interactions between a toxicant and target tissues that are undergoing biochemical changes. Damage may not be evident until a later stage of development (DeRosa et al., 1998; Bigsby et al, 1999). The brain, for example, is an organ with distinct neurodevelopmental stages that occur in temporally distinct time frames across different regions, so the specific chemical, dose, and time of exposure during development determine if a specific function in the brain will be altered (Faustman et al, 2000).

Differences also exist between children and adults with respect to their absorption, distribution, metabolism, and elimination of chemical contaminants. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC, 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman PL, 1974; Fomon, 1966; Fomon *et al*. 1982; Owen G.M., 1966; Widdowson E.M., 1964). The infant also has an immature blood-brain barrier (Adinolfi, 1985) (Johanson, 1980) and probably an immature blood-testis barrier (Setchell B.P., 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori *et al*. 1990; Leeder and Kearns, 1997; NRC, 1993; Vieira *et al*. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns, who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman PL, 1974; NRC, 1993; West J.R., 1948). Children and adults may differ in their capacity to repair damage from chemical insults.

OEHHA faces an additional challenge when evaluating chemicals that are potential endocrine disruptors. The topic of endocrine disruption during development has been the subject of much scientific and regulatory debate (Colborn *et al*. 1993a; Colborn *et al*. 1993b; Cranmer *et al*. 1984; US EPA, 1998). While not all chemicals selected for the OEHHA review are endocrine disruptors, the endocrine disruptors do pose a greater concern because not only could they directly impact the maturation and proper

functioning of the endocrine system, they could also interfere with hormonal signal transduction that leads to abnormal growth and functioning of other target organs (e.g., immune and nervous systems) in school children. Exposure to endocrine disruptors during critical "programming" periods in development, in contrast to exposure during adulthood, may produce irreversible effects on the reproductive, nervous, and/or immune systems (Bigsby *et al*. 1999). In adulthood, these endocrine disruptors might only produce reversible effects by participating in the "seesaw" process of stimulation and feedback inhibition.

Given the complexity of hormone signaling processes, it is also not surprising to find the evaluation of the dose and response relationship to be another challenge. The shape of the dose response curve may not be linear, but rather shaped like an upright U or an inverted U (Markowski *et al*. 2001; vom Saal *et al.* 1997). This makes data interpretation difficult when the study does not include sufficient treatment doses to span the entire range of interest.

In summary, the use of a study in children or young animals as the basis for a child-specific HGV is preferred. In cases when epidemiological studies involving an adult population, or studies involving adult animals, are used, the challenge is to integrate other experimental studies that suggest a greater sensitivity in the young with adult studies to justify the application of appropriate safety factors.

Process

In June 2002, OEHHA issued a report, "Development of Health Criteria for School Site Risk Assessment Pursuant to Health and Safety Code, Section 901(g): Identification of Potential Chemical Contaminants of Concern at California School Sites," documenting the process by which OEHHA identifies chemicals and presenting a compilation of 78 chemicals. The report can be found at http://www.oehha.ca.gov/public_info/public/kids/schoolsrisk.html. The compilation, whose sole purpose is to provide OEHHA staff with a manageable list of chemicals to work from, has no regulatory status and is a living document – chemicals may be added or removed as new information becomes available.

The chRD development process begins with the prioritization of chemicals from the compilation described in the June 2002 report. OEHHA has employed the following criteria, recognizing that often the availability of health effect data may be the overriding consideration in the selection of chemicals for evaluation.

1. Chemicals having a strong indication of their presence at school sites according to monitoring studies or other reliable sources.

2. Chemicals cited to have possible adverse effects in three or more of the systems that are undergoing critical development during childhood: the nervous, immune, respiratory, reproductive, or endocrine systems.

3. Chemicals that other OEHHA programs have identified as a concern.

From a public health protection standpoint, the OEHHA scientists working on health guidance values for children as mandated by Health & Safety Code 901(g) have adopted the following procedures in evaluating and developing chRDs or chRCs. First, in order to protect children from infancy through the time they leave school, chRDs must consider school-aged children up to age 18, and infants and toddlers in daycare facilities located at school sites. Second, OEHHA opts to consider the most sensitive species and endpoints in our evaluations. When evaluating various studies that use different test parameters to measure the same endpoint such as the nervous system, the lowest LOAEL (lowest observed adverse effect level) or NOAEL (no observed adverse effect level) from these studies would be selected. Third, the paucity of data has underscored the reality that the databases for sensitive endpoints may be incomplete. An uncertainty factor for database deficiency will be considered when there is sufficient information to suggest child-specific sensitivity but insufficient quantitative data from young animal studies to permit the use of these data. Fourth, because quantifying differences in susceptibility between a developing organ system and a mature one are hampered by the availability of studies that intentionally compare an effect in young animals with one in adult animals and available data are mainly from developmental toxicity studies that limit dosing to the mother during pregnancy, OEHHA staff have deemed that these studies can be used for development of a child-specific health guidance value (chRD or chRC) if it is reasonable to assume that the effect of the chemical on the target organ in the offspring animal would likely occur on the same target organ undergoing development after birth in humans. If studies that include gestational dosing of the mother and lactational dosing of the pups (a protocol of the U.S. EPA Developmental Neurotoxicity Health Effects Test) are available, OEHHA will also consider these studies acceptable for establishing a chRD or chRC if the development of the critical organ system continues to occur during childhood.

Finally, these prenatal and perinatal studies are frequently part of a series of studies to elucidate a "mechanism of toxicity". These studies may not have used a large number of animals or dose ranges. However, due to the critical windows in which cell proliferation and differentiation are occurring in specific organ systems during childhood, a study in young animals is usually preferred over one in adults, even adult humans. With corroborating studies showing a mechanism of action and biological plausibility, OEHHA will consider using these studies as appropriate. However, data from adult animals may be used, if they are from high quality studies and if there are data to provide a means of inference to vulnerability of development in young animals so that an appropriate uncertainty or safety factor can be applied.

Status

In December 2005, OEHHA issued a final report establishing chRDs for the first six evaluated chemicals: cadmium, chlordane, heptachlor, heptachlor epoxide, methoxychlor, and nickel, which can be found at:
http://www.oehha.ca.gov/public_info/public/kids/schools1205.html

Between 2003 and 2004, OEHHA selected 19 chemicals for which literature searches were performed. These chemicals included endosulfan, manganese, pentachlorophenol, toluene, lead, arsenic, aldrin, atrazine, DDE, DDT, dieldrin, endrin, hexachlorobenzene,

lindane, malathion, perchloroethylene, permethrin, selenium, and trichloroethylene. The Public Health Library at the University of California at Berkeley assisted in literature search. OEHHA, in turn, reviewed the citations and abstracts, and evaluated relevant qualitative papers and quantitative studies. As a result, OEHHA issued individual draft reports recommending a chRD for endosulfan, manganese, pentachlorophenol, toluene, and lead.

In the 2004-2005 cycle, atrazine and deltamethrin are two of the chemicals selected for an in-depth review. This draft document provides a summary on OEHHA's evaluation of atrazine and deltamethrin pursuant to Health and Safety Code Section 901(g).

DRAFT

References

Adinolfi, M. (1985) The development of the human blood-CSF-brain barrier. *Dev Med Child Neurol*;27(4):532-7.

Altman PL (1974) *Biological handbooks: Biology data book.* III, 2nd Ed.: pp 1987-2008.

Bigsby, R., Chapin, R. E., Daston, G. P., Davis, B. J., Gorski, J., Gray, L. E., Howdeshell, K. L., Zoeller, R. T., and Vom Saal, F. S. (1999) Evaluating the effects of endocrine disruptors on endocrine function during development. *Environ Health Perspect*;107 Suppl 4:613-8 .

Colborn T, Vom Saal F S and Soto A M (1993) Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans [See Comments]. *Environ Health Perspect* 101: pp 378-84.

Cranmer JM, Cranmer M F and Goad P T (1984) Prenatal Chlordane Exposure: Effects on Plasma Corticosterone Concentrations Over the Lifespan of Mice. *Environ Res* 35: pp 204-10.

Fomon JS (1966) Body Composition of the Infant: Part I: The Male "Reference Infant". *Faulkner F, ed. Human development.* pp 239-246.

Fomon, J. S., Haschke, F., Ziegler, E. E., and Nelson, S. E. (1982) Body composition of reference children from birth to age 10 years. *Am J Clin Nutr*;35(5 Suppl):1169-75.

Johanson, C. E. (1980) Permeability and vascularity of the developing brain: cerebellum vs cerebral cortex. *Brain Res*,190(1):3-16.

Komori, M., Nishio, K., Kitada, M., Shiramatsu, K., Muroya, K., Soma, M., Nagashima, K., and Kamataki, (1990) T. Fetus-specific expression of a form of cytochrome P-450 in human livers. *Biochemistry* 29[18], 4430-3.

Leeder, J. S. and Kearns, G. L. (1997) Pharmacogenetics in pediatrics. Implications for practice. *Pediatr Clin North Am* 44[1], 55-77.

Markowski VP, Zareba G, Stern S, Cox C and Weiss B (2001) Altered Operant Responding for Motor Reinforcement and the Determination of Benchmark Doses Following Perinatal Exposure to Low- Level 2,3,7,8-Tetrachlorodibenzo-p-Dioxin. *Environ Health Perspect* 109: pp 621-7.

Morselli, P. L., Franco-Morselli, R., and Bossi, L. (1980) Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. *Clin Pharmacokinet*;5(6):485-527.

NRC (1993) Pesticides in the Diets of Infants and Children. *National Research Council.*

National Academy Press. .

Owen G.M. BJ (1966) Influence of Age, Sex, and Nutrition on Body Composition During Childhood and Adolescence. *Falkner F, ed. Human development.* pp 222-238.

Selevan SG, Kimmel C A and Mendola P (2000) Identifying Critical Windows of Exposure for Children's Health. *Environ Health Perspect* 108 Suppl 3: pp 451-5.

Setchell B.P. WGMH (1975) The Blood-Testis Barrier. *Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V*.

US EPA (1997) Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis. Crisp, TM, Clegg, ED, Cooper, RL, and Anderson et al.

US EPA (1998) Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) Final Report. Washington DC.

Vieira, I., Sonnier, M., and Cresteil, T. (1996) Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem*;238(2):476-83.

vom Saal FS, Timms B G, Montano M M, Palanza P, Thayer K A, Nagel S C, Dhar M D, Ganjam V K, Parmigiani S and Welshons W V (1997) Prostate Enlargement in Mice Due to Fetal Exposure to Low Doses of Estradiol or Diethylstilbestrol and Opposite Effects at High Doses. *Proc Natl Acad Sci U S A* 94: pp 2056-61.

West J.R. SHWCH (1948) Glomerular Filtration Rate, Effective Renal Blood Flow, and Maximal Tubular Excretory Capacity in Infancy. *Journal of Pediatrics* 32: pp 10-18.

WHO (2002) Global Assessment of the State-of-the-Science of Endocrine Disruption. Damstra, T, Barlow, S, Bergman, A, Kavlock, R, and Van Der Kraak, G. . World Health Organization.

Widdowson E.M. DJWT (1964) Chemical Composition of the Body. *C.L. Comar and Felix Bronner, eds. Mineral metabolism: An advanced treatise, Volume II : The elements part A.*

Ziegler, E. E., Edwards, B. B., Jensen, R. L., Mahaffey, K. R., and Fomon, S. J. (1978) Absorption and retention of lead by infants. *Pediatr Res*;12(1):29-34.

Atrazine

Summary

OEHHA has identified atrazine as a contaminant of concern pursuant to Health and Safety Code Section 901(g). In an updated review of available literature, OEHHA has not found additional critical studies with a NOAEL or LOAEL that is comparable to, or lower than, those used in establishing the existing health criteria, which could serve as a basis for developing a child-specific reference dose (chRD) for atrazine. OEHHA determines that it is appropriate to apply the same NOAEL used to calculate a Public Health Goal (PHG) for the non-cancer endpoint in establishing a chRD of 0.005 mg/kg-day for assessing the non-cancer risk of atrazine at existing or proposed school sites.

What is atrazine?

Atrazine, 6-chloro-N-ethyl-N'-(1-methylethyl)-triazine-2,4-diamine, is a herbicide that is widely used to kill weeds. It is used in agricultural areas and on highway and railroad right-of-way for weed control (ATSDR, 2003). Table 1 provides a summary of atrazine use in California. The data do not indicate an increasing or a decreasing use trend, but rather, suggest a sustained use of atrazine.

Table 1

Atrazine Use Trend in California Pesticide Use Report, California Department of Pesticide Regulation							
	POUNDS APPLIED						
	1997	1998	1999	2000	2001	2002	2003
ATRAZINE	48,482	57,003	72,175	57,403	62,872	59,292	58,245

What characteristics make atrazine of concern pursuant to Health & Safety Code Section 901 (g)?

OEHHA has identified atrazine as a contaminant of concern pursuant to HSC 901(g) (OEHHA, 2002). Atrazine is of concern to schoolchildren because available data indicate that atrazine could adversely impact the development of both the male and female reproductive systems. Various animal studies have shown that atrazine affects the

hypothalamus, pituitary, gonads, and/or pubertal maturation. In addition, atrazine could potentially affect the cardiovascular, immune, and nervous systems.

Atrazine is also likely to be found at school sites that have a history of agricultural activities. While atrazine is relatively mobile in the surface soil, it becomes immobilized once leached into the subsoil and degrades slowly (OEHHA, 1999). No leaching of atrazine or its metabolites was observed below soil layers of 15-30.5 cm in California, Minnesota, and Tennessee soils (U.S. EPA, cited in OEHHA, 1999). Thus, atrazine may accumulate in upper subsoil layers after years of its application. Atrazine has been found in current or former National Priorities List (NPL) sites (ATSDR, 2003). ATSDR notes that the total number of NPL sites evaluated for this herbicide is not known. However, ATSDR feels that the number of sites with atrazine found would increase as more atrazine sampling and analysis are performed. Likewise, the total of school sites evaluated for atrazine is not known; nevertheless, it will likely be found as more atrazine sampling and analysis is included.

What are the existing health guidance values for atrazine?

U.S. EPA Reference Dose (RfD)

U.S. EPA has established an RfD of 0.035 mg/kg-day for atrazine (U. S. EPA., 1987). The RfD is based on a 1986 Ciba-Geigy study involving Sprague-Dawley rats. Dietary doses of 0, 0.5, 3.5, 25 and 50 mg/kg-day of atrazine were given to rats (20/sex/dose) for two years. Mean body weights were significantly depressed ($p<0.01$) in males and females receiving 25 and 50 mg/kg-day of atrazine. Based on decreased body weight gain, the LOAEL for systemic toxicity is 25 mg/kg-day and the NOAEL 3.5 mg/kg-day. U.S. EPA applied an uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) to the NOAEL in calculating the RfD.

U.S. EPA Health Criteria

More recently, U.S. EPA has established two health criteria for use in a human health risk assessment in support of the re-registration eligibility decision for atrazine (U.S. EPA, 2002c). These health criteria are based on a study on adult rats, which evaluated the effect of atrazine exposure on the proestrus luteinizing hormone (LH) surge (Morseth, 1996). Atrazine, 97.1 percent a.i., was administered to 360 female Sprague Dawley rats in the diet for 26 weeks (approximately six months). Dose levels were 0 (negative control), 25, 50, and 400 parts per million (ppm) (0, 1.80, 3.65, 29.44 mg/kg/day). Body weight, body weight gain and food consumption were significantly ($p\leq0.05$) decreased in animals at the high dose tested compared to controls (body weight decreased 8.5 percent at the end of the study and food consumption decreased 3.75 percent for the entire study). The percentage of days in estrus was significantly increased ($p\leq0.01$) during the 21-22 and 25-26 week time periods at the high-dose level. Percent days in estrus were also increased during the 21-22 and 25-26 week time periods at the mid dose, but the increase was only significant ($p\leq0.05$) for the 21-22 week time period. The proestrus afternoon

LH surge was severely attenuated at the high dose (LH levels at most sampling time points were actually decreased compared to baseline) and less so at the mid dose (maximum increase in the mid dose group over baseline was 157% compared to maximum increase over baseline in controls of 273%). Pituitary weights were increased at the high dose (absolute weight increased 22% and weight relative to body weight was increased 28%). Pituitary weights at the other two doses were not affected. At the high dose, there was a slight increase in animals displaying enlarged pituitaries (0% in controls compared to 3.4% at 29.44 mg/kg/day) and thickened mammary glands (0% in controls compared to 6.7% at 29.44 mg/kg/day). There were no other gross necropsy findings in the high dose that could be attributed to compound exposure and there were no compound-related gross pathology findings at the mid- or low-dose. Selected tissues were saved for histopathology but those results have not been reported. There were no compound-related effects in mortality or clinical signs. The proestrus afternoon prolactin surge was not affected by compound exposure at any dose. The low dose had no effects on the estrous cycle, LH or prolactin surges. U.S. EPA determines that the LOAEL is 3.65 mg/kg-day and the NOAEL is 1.8 mg/kg-day based on estrous cycle alterations and LH surge attenuation.

The NOAEL of 1.8 mg/kg-day was used in conjunction with uncertainty and child safety factors to calculate the two health criteria—one for assessing dietary (including drinking water risk and the second for assessing the risk from oral ingestion of, or dermal contact with, contaminated soil. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) was uniformly applied; however, a different child protection factor was applied in developing the dietary and the soil health criteria. U.S. EPA's Health Effects Division (HED), Food Quality Protection Act (FQPA) Safety Factor Committee (SFC) determined that there is not sufficient reliable data to assign a different safety factor than the10X default factor to dietary exposure scenarios but that there is reliable data demonstrating that the safety of infants and children will be protected by use of an additional safety factor of 3X for soil exposure scenarios (U.S. EPA, 2002b).

The following is a summary of U.S.EPA's analysis in support of its respective 3X and 10X factor determinations. Other atrazine testing using young rats has been limited to short periods of dosing in specific developmental periods. Uncertainties are raised for susceptibility during earlier developmental periods as well as for consequences of earlier developmental exposure with longer duration of dosing throughout development. The effects of neurotransmitters/peptides (known to be critical for normal development and which could potentially translate into severe effects in children that may not be manifested until later in life) have not been fully characterized. As the Federal Insecticide Fungicide Rodenticide Act (FIFRA) Scientific Advisory Panel noted, there are concerns for behavioral effects in the young resulting from atrazine's mode of action on the nervous system and the dose level at which these effects might occur.

U.S. EPA used the following rationale to conclude that an additional Special FQPA Safety Factor of 3X would be adequate to account for the above concern. The toxicology endpoints reviewed (e.g., delayed puberty in males and females, suppressed LH surge, and decreasing hypothalamic norepinephrine (NE) and gonadotropin releasing hormone

(GnRH), to be elaborated in the next section) are all consistent with atrazine's mode of action on the neuroendocrine system. Using the most sensitive endpoint with the lowest NOAEL (1.8 mg/kg-day) as a basis for the health criteria is appropriate, albeit that this NOAEL is derived from an adult rat study. When comparing the effects observed in adults to those observed in the young, U.S. EPA noted that clear NOAELs were established for delayed puberty in both male and female offsprings (6.25 mg/kg-day in males; 12.5 mg/kg-day in females). If the lowest offspring NOAEL from this study is protected by a factor of 3X, the extrapolated NOAEL is 2.0 mg/kg-day. Comparing this value to the adult NOAEL of 1.8 mg/kg-day from the 6-month LH Surge study indicates that the young are not likely to be an order of magnitude more sensitive than the adult. A 3X safety factor applied to the NOAEL from the adult study would provide infants and children with an order of magnitude (10X) level of protection from the lowest offspring NOAEL. Therefore, U.S. EPA concluded that, given the half-log (3X) protection provided children by the more sensitive endpoint in adults and the relatively tight pattern of NOAELs for adults and children from existing studies, a half-log reduction in the default Special FQPA Safety Factor (3X) is considered to be sufficiently protective of the concerns for this CNS mode of action in the young.

Regarding the dietary (including drinking water) scenario, U.S. EPA concluded that the default 10X FQPA safety factor is statutorily required in the absence of reliable evidence showing that a safety factor different than the statutory 10X default would be protective of infants and children. In addition to the neuroendocrine uncertainties, U.S. EPA felt that there are data gaps especially pertaining to the extent of atrazine exposure via drinking water. Although it is known that there is significant, widespread exposure to atrazine and its metabolites in drinking water, limitations in the extent, frequency, and compounds tested for in the monitoring data raise significant uncertainties regarding the level of exposure to atrazine and its metabolites. On that basis, U.S. EPA felt the statutorily mandated 10X factor should be applied in developing the health criterion for the dietary and drinking water scenario.

Using the NOAEL of 1.8 mg/kg-day, an uncertainty factor of 100, and a safety factor of three or 10, U.S. EPA has developed a health criterion of 0.006 mg/kg-day for the soil scenario and a criterion of 0.002 for the dietary/drinking water scenario.

ATSDR Minimal Risk Level (MRL)

ATSDR (2003) has established a MRL of 0.003 mg/kg/day, which was derived from a 19-day pig study (Gojmerac *et al*. 1999). Groups of nine female Swedish Landrace/Large Yorkshire cross pigs (6–7-month-old gilts) were administered 0 or 1 mg/kg-day atrazine in the feed for 19 days beginning with the onset of estrus (day 0). Blood samples were drawn three times daily at 3-hour intervals on five post-treatment days (this corresponded to the two days before [days -1 and -2] the next estrus, the expected day of the next estrus [day 0], and two days [days 1 and 2] after the expected estrus). Serum 17β-estradiol (E2) concentrations in the blood samples were determined, and histopathological examination of the uterus was performed. E2 concentrations were statistically significantly different ($p<0.001$) from controls on all five days measured. In controls, E2 concentrations were

high on days -2 and -1, then dropped on day 0 (beginning of estrus) and remained low on days 1 and 2. In treated animals, E2 concentrations were lower than controls on days -2 and -1, and higher than controls on days 0 through 2. Treated pigs failed to exhibit overt signs of estrus onset and uterine histopathology indicated a state of uterine rest (diestrus) at the end of the observation period. A slight, but steady increase of E2 hormone level was seen in the treated animals on day 24 of the estrus cycle (day 2). The authors suggested that the balance of the E2 hormone level was being gradually restored, which is the pattern that would be anticipated if the animals were about to go into estrus. Similar results were seen after administration of 0 or 2 mg/kg/day atrazine (Gojmerac *et al*. 1996). The oral MRL of 0.003 mg/kg-day was calculated based on the LOAEL of 1.0 mg/kg-day and an uncertainty factor of 300 (10 for LOAEL to NOAEL conversion, 10 for extrapolation from animals to humans, and 3 for human variability). An uncertainty factor of three for human variability was used instead of 10 because the critical effect was identified in a sensitive population (young, developing female pigs).

CDPR Risk Characterization

CDPR has issued a risk characterization document in support of its regulatory activity on atrazine (CDPR, 2001a). A chronic NOAEL of 0.48 mg/kg-day (rounded to 0.5 mg/kg-day) was identified from a dog study for use in the risk assessment. As discussed below, OEHHA used the same study in deriving a PHG for the non-cancer endpoint. Gammon et al. recently reviewed the human health and ecological aspects of atrazine use in California (Gammon et al., 2005). That review also supports the use of this chronic NOAEL.

OEHHA Public Health Goal (PHG)

OEHHA has developed a cancer-based PHG of 0.00015 mg/L (0.15 μg/L or 0.15 ppb) for atrazine in drinking water (OEHHA, 1999). In that process, OEHHA also reviewed non-cancer endpoints of atrazine. The most sensitive endpoint identified was cardiomyopathy, observed in a one-year dog study (O'Connor et al., 1987). This is the same study the CDPR used in characterizing the chronic, non-cancer risk of atrazine (CDPR, 2001a). Atrazine (97 percent) was given to 5-month-old, pre-pubertal, beagles (6 dogs/sex in the control and high dose groups; and 4 dogs/sex in the low-and mid dose groups) for one year at dietary levels of 0, 15, 150, and 1000 parts per million (ppm) (equivalent to male: 0, 0.48, 4.97, and 33.65 mg/kg-day; female; 0, 0.48, 4.97 and 33.8 mg/kg-day). Three animals were killed during the study in moribund condition: one 150 ppm male on day 75; one 1000 ppm female on day 113 and one 1000 ppm male on day 250. Cardiopathy (discrete myocardial degeneration) was the most significant effect observed in animals fed 1000 ppm. Clinical signs associated with cardiac toxicity were: ascites, cachexia, labored/shallow breathing, and abnormal EKG (irregular heart beat and increased heart rate, decreased P-II values, atrial premature complex, atrial fibrillation). These were first observed as early as 17 weeks into the study. Gross pathological examination revealed moderate-to-severe dilation of the right atrium (and occasionally the left atrium), microscopically manifested as atrophy and degeneration of the atrial

myocardium. Other effects observed were: decreased food consumption and body weight gain at 1000 ppm, decreased red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), total protein and albumin, as well as an increase in platelet counts, P, Na, glucose and liver and ovary relative weights at 1000 ppm. The authors of the study concluded that 150 ppm (4.97 mg/kg-day) was the NOAEL. However, CDPR, in analyzing the data, came to the conclusion that the NOAEL is 15 ppm (0.48 mg/kg-day) (CDPR, 2001b). The following is an excerpt of CDPR's toxicological summary:

> "At 150 and 1000 ppm, females experienced increased heart weights and in both sexes treatment related electrocardiographic changes in the heart accompanied by gross and histologically detectable pathology were observed. Previously reviewed as having a NOAEL of 15 ppm (Silva, 5/20/88), the study has been re-evaluated based upon information submitted to CDPR by Ciba-Geigy. The status, however, remains unchanged."

OEHHA adopted CDPR's analysis as a basis for calculating a potential PHG for the non-cancer endpoint. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) was applied to the NOAEL of 0.48 mg/kg-day in calculation.

What data indicate a critical effect of atrazine in school-age children?

Reviews performed by ATSDR, U.S. EPA, and CDPR (ATSDR, 2003; U.S. EPA, 2002c; and CDPR, 2001a) were examined to establish a baseline for atrazine's non-cancer effects on humans, particularly children. There were a number of worker incidences reported. It appears that the majority of cases involved skin illnesses such as dermal irritation and pain, rashes, and welts; and eye illnesses such as eye damage, blurred vision, conjunctivitis, irritation, and pain. Incidences involving children were also reported. Dermal and ocular effects accounted for the majority of symptoms associated with exposure to atrazine, though a few cases also reported gastrointestinal, neurological, and respiratory effects. Moreover, OEHHA examined available literature and did not locate any additional human studies. Because there are so few studies on humans and the exposure levels are usually unknown, OEHHA depends primarily on animal data to assess the potential effects of atrazine on children.

Atrazine could adversely impact the hepatic, renal, cardiovascular, immune, nervous, or reproductive system (ATSDR, 2003; OEHHA, 1999). Potential effects on the cardiovascular, immune, nervous or reproductive system are of special concern to young children because these organ systems are still undergoing development, and thus are vulnerable to chemical injuries. Data on young animals indicate that the reproductive system is a primary target. Most of the existing health criteria are based on an endpoint that indicates an effect on the reproductive system. Atrazine affects both the male and female reproductive systems. Rat studies have demonstrated that atrazine induced a delay in female sexual maturation (Ashby *et al*. 2002; Laws *et al*. 2000). In the Laws study, female Wistar rats were dosed by oral gavage from postnatal days 22 thorough 41 with 0, 12.5, 25, 50, 100 or 200 mg/kg of atrazine. Vaginal opening, an indicator of female sexual maturation, was significantly delayed in a dose-dependent manner. A

similar observation on the delay of vaginal opening was made in the Ashby study. In discussing the mechanism of toxicity, U.S.EPA cited several studies in proposing that atrazine acts on the hypothalamic-pituitary-ovarian axis (U.S.EPA, 2002a). Atrazine affected the hypothalamus, leading to a decreased secretion of hypothalamic norepinephrine and a decreased release of gonadotropin releasing hormone (GnRH) (Cooper *et al*., 1998). Atrazine caused an attenuation of luteinizing hormone (LH) surge (presumably via its action on the hypothalamus) (Cooper *et al*., 2000; Morseth, 1996). Perturbation of LH, in turn, affected the aforementioned pubertal development.

Studies have also shown that atrazine could adversely impact the male reproductive system. Serum and intra-testicular levels of testosterone were significantly reduced when juvenile male rats were exposed to atrazine by gavage (Friedmann, 2002); the ventral prostate and seminal vesicle weights of peripubertal rats were reduced (Trentacoste *et al.,* 2001); and preputial separation, an indicator of male sexual maturation, was also delayed in atrazine treated juvenile rats (Stoker *et al*., 2000).

Which study should be used as a basis for establishing the child-specific reference dose for atrazine?

From literature search and review, OEHHA did not find additional critical studies with a NOAEL or LOAEL that is comparable to, or lower than, those used in establishing the existing health criteria, which could serve as a basis for developing a child-specific reference dose for atrazine. Table 2, which presents these existing health criteria and a potential chRD, provides a framework for discussion.

Table 2

	Health Criteria (mg/kg-day)	Inter-species Factor	Intra-species Factor	LOAEL-to-NOAEL Factor	Child Safety Factor	LOAEL* or NOAEL** (mg/kg-day)	Study	Endpoint
U.S. EPA RfD	0.035	10	10	1	1	3.5**	2 yr rat	Decreased body weight gain
U.S. EPA Criterion for dietary assessment	0.002	10	10	1	10	1.8**	6 mo female rat	attenuation of LH surge

U.S. EPA Criterion for residential assessment	0.006	10	10	1	3	1.8**	6 mo female rat	attenuation of LH surge
ATSDR MRL	0.003	10	3	10	1	1*	19 day gilts	Decreased estrogen levels; delayed onset of estrus
Potential chRD derived from PHG calculation	0.005	10	10	1	1	0.48**	1 yr juvenile dogs	Increased heart weight ; myocardio pathy

OEHHA would not recommend using U.S. EPA's RfD because the study endpoint, body weight, is not a good measure of potential critical effects on children. Moreover, the numerical value of the RfD is the highest (least protective) among those values compared. While U.S. EPA's health criterion for dietary assessment (in support of the re-registration eligibility decision for atrazine) is most health protective, OEHHA feels that the use of this criterion is not appropriate in the context of school-site risk assessment. OEHHA concurs with U.S. EPA that the application of a 3X child safety factor would suffice. However, because the health criterion was intended for dietary assessment, U.S. EPA was statutorily required to use the default 10X FQPA safety factor in the absence of scientific certainty. The school-site risk assessment program does not pertain to dietary assessment and is not subject of FQPA. As such, OEHHA would also not recommend using this health criterion, which is based on a 10X FQPA factor, for school-site assessment.

With respect to U.S. EPA's criterion for residential assessment (in support of the re-registration eligibility decision for atrazine), ATSDR's MRL, and the potential chRD, these values fall within a narrow range (0.003-0.006 mg/kg-day). The supporting studies and respective endpoints are relevant to children. The MRL is based on a study of immature female pigs. The potential chRD is based on a study of young dogs used by CDPR in its risk characterization document and by OEHHA in calculating a potential PHG for the non-cancer endpoint. While the health criterion for residential assessment is based on a study of adult rats, the young rat study cited by U.S. EPA support the view that the critical effect on the reproductive system observed in adult rats could also be triggered by atrazine in young animals. Thus, this adult rat study is pertinent to children.

Regarding the endpoints, atrazine's effects of the endocrine/reproductive system observed from the rat and gilt studies are clearly relevant. OEHHA feels that the cardiovascular (CV) effect observed in the dog study is also applicable. While CV system begins to develop within two weeks after conception and is one of first organ

systems to become functional, postnatal growth continues, which includes the hypertrophy of myocytes, increase in the number of DNA copies (polyploidy) in myocytes, and increase in capillary density (Penney, 2004). Postnatal development of the CV system could confer a critical window of vulnerability to chemical injury.

Both the dog and rat studies present a NOAEL; whereas, the pig study only confers a LOAEL. The former studies are preferred from this perspective. Because OEHHA has previously used the dog study as the basis for calculating a PHG for the non-cancer endpoint and a chRD based on the same study would also be protective of the endocrine/reproductive endpoint, OEHHA opts to use the dog study for developing the chRD. No additional safety factor for children is proposed for this chRD because the critical study used relatively young animals and the chRD as defined would be as protective as the U.S. EPA health criterion, which has incorporated a factor of three for protection of children, for an endocrine disruption endpoint. Calculation of this chRD is given below:

$$chRD = \frac{\text{NOAEL}}{\text{UF}} = \frac{0.48\ \text{mg/kg - day}}{100} = 0.005\ \text{mg/kg - day}$$

Where,

UF = Uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

Reference

Ashby, J., Tinwell, H., Stevens, J., Pastoor, T. and Breckenridge, C. (2002) The Effects of Atrazine on the Sexual maturation of Female Rats. *Regulatory Toxicology and Pharmacology* **35**, 468-473.

ATSDR (Agency of Toxic Substances and Disease Registry) (2003) Toxicological Profile of Atrazine. *U.S. Department of Health and Human Services*

CDPR (2001a) Atrazine:Risk Characterization Document.

CDPR (2001b) Summary of Toxicology Data--ATRAZINE.

Cooper, R.L., Stoker, T., McElroy, W. and Hein, J. (1998) Atrazine Disrupts Hypothalamic Catecholamines and Pituitary Function. *The Toxicologist* **42**, 160

Cooper, R., Stoker, T., Tyrey, L., Golman, J. and McElroy, W. (2000) Atrazine Disrupts the Hypothalamic Control of Pituitary-ovarian Function. *Tox. Sci.* **53**, 297-307.

Friedmann, A. (2002) Atrazine Inhibition of Testosterone Production in Rat Males following Peripubertal Exposure. *Reproductive Toxicology* **16**, 275-279.

Gammon, D., Aldous, C., Carr, W., Sanborn, J., and Pfeifer,K. (2005) A Risk Assessment of Atrazine Use in California: Human Health and Ecological Aspects. *Pest Manag. Sci.* **61**, 331-355.

Gojmerac, T., Kartal, B., Curic, S., Zuric, M., Kusevic, S. and Cvetnic, Z. (1996) Serum biochemical changes associated with cystic ovarian degeneration in pigs after atrazine treatment. *Toxicol Lett* **85**, 9-15.

Gojmerac, T., Uremovic, M., Uremovic, Z., Curic, S. and Bilandzic, N. (1999) Reproductive disturbance caused by an S-triazine herbicide in pigs. *Acta Vet Hung* **47**, 129-35.

Laws, S.C., Ferrell, J.M., Stoker, T.E., Schmid, J. and Cooper, R.L. (2000) The effects of atrazine on female wistar rats: an evaluation of the protocol for assessing pubertal development and thyroid function. *Toxicol Sci* **58**, 366-76.

Morseth, S. (1996) Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats--(Final) 6-Month Interim Report: Lab Project Number: CHV 2386-111: 2386-111: 6791E. Unpublished study prepared by Corning Hazleton Inc. 727 p

O'Connor, D., McCormick, G. and Green, J. (1987) Chronic Toxicity Study in Dogs: Atrazine Technical: Laboratory Study No. 852008.Unpublished study prepared by Ciba-Geigy Corp. 1405 p.

OEHHA (2002) Development of Health Criteria for School Site Risk Assessment Pursuant of Health and Safety Code 901(g): Identification of Potential Chemical Contaminants of Concern at California School Sites. *Office of Environmental Health Hazard Assessment,*

Cal/EPA, Final Report

OEHHA (Office of Environmental Health Hazard Assessment) (1999) Public Health Goal for Atrazine in Drinking Water. *California Environmental Protection Agency.*

Penney, D.G. (2004) Early Development of the CV System (http://www.coheadquarters.com/PennLibr/MyPhysiology/Mod21/indexdev2.htm).

Stoker, T.E., Laws, S.C., Guidici, D.L. and Cooper, R.L. (2000) The effect of atrazine on puberty in male wistar rats: an evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol Sci* **58**, 50-9.

Trentacoste, S., Friedmann, A., Youker, R., Breckenridge, C. and Zirkin, B. (2001) Atrazine Effects on Testosterone Levels and Androgen-Dependent Reproductive Organs in Peripubertal Male Rats. *Journal of Andrology* **22**, 142-148.

U. S. EPA. (1987) Atrazine (CASRN 1912-24-9). *IRIS (Intergrated Risk Information System).*

U.S.EPA (2002a) The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity.

U.S. EPA (2002b) *ATRAZINE/DACT* - Reassessment Report of the FQPA Safety Factor Committee. TXR NO. 0050638

U. S. EPA (2002c) Revised Human Health Risk Assessment for the Reregistration Eligibility Decision: Atrazine.

DRAFT

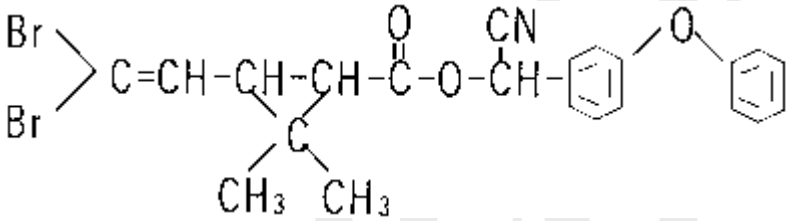
Deltamethrin

Summary

OEHHA has identified deltamethrin as a contaminant of concern pursuant to Health and Safety Code Section 901(g). OEHHA has reviewed available data in developing a chRD for deltamethrin for school site risk assessment. The nervous system is the primary target for deltamethrin toxicity. Available information indicates that neurotoxicity is the most sensitive endpoint, and OEHHA is recommending a chRD of 0.0001 mg/kg-day for deltamethrin based on that endpoint.

What is deltamethrin?

Deltamethrin is a type II pyrethroid insecticide, with the following structural formula:



The pyrethroids are synthetic chemicals with structure similar to the pyrethrins, which are naturally occurring chemicals found in certain chrysanthemum flowers. The pyrethroids are generally more toxic to insects and mammals, and more persistent in the environment than pyrethrins (ATSDR, 2003). The type II pyrethroids are generally characterized by having a cyano group in the structure; and by producing effects that may include pawing and burrowing behavior, salivation, increased startle response, abnormal hindlimb movements, and coarse whole body tremors that progress to sinuous writhing (choreoathetosis).

In addition to being manufactured as a pesticide, deltamethrin is also a breakdown product of tralomethrin, another pyrethroid. Environmental fate studies have indicated that tralomethrin is unstable under either an aerobic or anaerobic condition, and rapidly undergoes debromination to form deltamethrin (CDPR, 2000).

Table 1 summarizes the use trend of deltamethrin in California. The data indicate that deltamethrin is largely used in structural pest control, and its use has increased by an 80 fold in six years. Other uses include the treatment of cotton, non-food/feed areas of food/feed processing plants, granaries, and ornamental plants (CDPR, 2000).

Table 1

Deltamethrin Use Trend in California Pesticide Use Report, California Department of Pesticide Regulation						
	POUNDS APPLIED					
	1998	1999	2000	2001	2002	2003
STRUCTURAL PEST CONTROL	212	3,305	10,606	17,107	12,458	17,690
Chemical Total	214	3,343	10,910	17,721	13,001	18,301

What characteristics make deltamethrin of concern pursuant to Health & Safety Code Section 901 (g)?

The nervous system is a primary target for deltamethrin toxicity. Its potential effects on the developing brain in children are of concern.

A recent California portable classroom study has identified deltamethrin and tralomethrin as contaminants in floor dust (ARB and DHS, 2003). Floor dust from 39 portable classrooms and 38 traditional classrooms were analyzed. Deltamethrin/tralomethrin were detected in 29 percent of the portable classrooms and 39 percent of the traditional classrooms. Contaminated floor dust is especially a concern in rooms used by very young children, who spend a substantial amount of time on the floor and may be exposed to deltamethrin through ingestion, inhalation, and even through dermal absorption. Carpets can serve as a reservoir of dust and particles.

What are the existing health guidance values for deltamethrin?

U.S. EPA Health Criterion for Chronic Dietary Risk Assessment

U.S. EPA, in 40 Code of Federal Regulations, Part 180, establishes tolerance levels for deltamethrin on a number of agricultural commodities (U.S. EPA, 2004). U.S. EPA summarized those guideline and non-guideline studies that the agency had reviewed in defining a chronic NOAEL of 1.0 mg/kg-day from a dog study (Ryle et al., 1993) for use in a dietary assessment to support the promulgated tolerance levels. In the Ryle study, beagles (4 males and 4 females per group) were orally dosed with a capsule containing 0, 1, 10 or 50 mg/kg-day of deltamethrin for 52 weeks. The increased incidences of chewing and scratching of extremities, and liquid feces were observed in the higher dose groups and U.S. EPA determined that 1.0 mg/kg-day is the NOAEL. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies) and a 3X Food Quality Protection Act (FQPA) safety factor based on difference in brain concentration of deltamethrin between weanling and adult rats (Sheets et al., 1994) were applied to the NOAEL in developing the health criterion of 0.003 mg/kg-day for the dietary risk assessment.

ATSDR Minimal Risk Level (MRL)

In the draft Toxicological Profile for Pyrethrins and Pyrethroids, the Agency for Toxic Substances and Disease Registry (ATSDR) proposes a MRL of 0.002 mg/kg/day for deltamethrin (ATSDR, 2001). This MRL is based on results of a study that indicate altered motor behavior in adult mice treated with deltamethrin neonatally (Eriksson and Fredriksson, 1991). However, ATSDR withdrew this MRL from the final Toxicological Profile (ATSDR, 2003), noting that other investigators (Ray et al. 2002) were unable to replicate the results of the Eriksson study.

In the 1991 Eriksson study, groups of 10-day-old male NMRI mice were treated with 0 (vehicle control) or 0.7 mg deltamethrin/kg in a fat emulsion vehicle by gavage daily for seven consecutive days. Following treatment cessation, 17-day- and 4-month-old mice were tested for spontaneous behavior (locomotion, rearing, and total activity). Tests were conducted for one hour, and scores were summed for three 20-minute periods. Behavior in the 17-day-old mice was not significantly different from that in controls. However, when tested at four months of age, deltamethrin-treated mice exhibited significantly increased locomotion and total activity during the last 20 minutes of the test period. This was interpreted as disruption of a simple, non-associative learning process, (i.e., habituation), or a retardation in adjustment to a new environment. Receptor assays, performed one–two weeks following behavioral testing at four months of age, revealed a significant trend toward a decrease in muscarinic acetylcholine (MACh) receptor density in the cerebral cortex of deltamethrin-treated mice. No significant treatment-related changes in this parameter were seen in two other brain regions, the hippocampus and striatum. The authors concluded that disturbances of the cholinergic system during rapid development in the neonatal mouse could lead to permanent changes in cholinergic and behavioral variables in the animals as adults.

As observed by ATSDR, the study shows that oral exposure of neonatal mice to deltamethrin levels below those resulting in overt signs of acute neurotoxicity may cause changes in receptor densities within the brain that can be observed at maturation. Neonatal exposure can also cause changes in behavioral patterns that are first apparent in adulthood. On that basis, the LOAEL of 0.7 mg/kg-day is divided by an uncertainty factor of 300 (10 for LOAEL-to-NOAEL conversion, 10 for interspecies extrapolation and three for human variability; three instead of 10 for human variability was used because ATSDR feels that the neonatal mouse is a sensitive subject.) to derive the proposed MRL.

CDPR Risk Characterization

In its Risk Characterization Document for deltamethrin, the California Department of Pesticide Regulation (CDPR) identified both acute/sub-chronic and chronic No Observed Effect Levels (NOELs) for calculating margins of exposure (MOE)(CDPR, 2000). An MOE is defined as the ratio of absorption-adjusted NOEL to the estimated human absorbed dose. MOEs are calculated for various exposure scenarios.

An acute/subchronic LOEL of 0.1 mg/kg-day and an estimated acute/subchronic NOEL of 0.01 mg/kg-day were identified based on a 13-week oral study in dogs (Chesterman, 1977). Deltamethrin was dissolved in a solvent and inserted into gelatin prior to administration. Treatment doses were 0, 0.1, 2.5, or 10 mg/kg-day. Three animals/sex/group were used for controls and 0.1 mg/kg-day. All other dose groups had five animals per sex. The endpoints including liquid feces, vomiting, and tremors, which are characteristic of autonomic nervous system dysfunction, were reported during the first week of treatment.

A chronic NOEL of 0.1 mg/kg-day was identified based on a two-year oral study in rats (Goldenthal, 1980). Deltamethrin without a solvent carrier was administered in the feed to Sprague-Dawley rats at levels of 0, 2, 20 or 50 ppm (equivalent to 0, 0.11, 1.1, or 2.8 mg/kg/day). Ninety animals per sex per dose were used, with 10 animals/sex /dose for interim sacrifice at 6, 12, and 18 months. Dose-related increases in the degeneration of sciatic, tibial, and plantar nerves were observed at 18 months.

What data indicate a critical effect of deltamethrin in children?

Reviews of human data and illness reports by CDPR (CDPR, 2000) and ATSDR (ATSDR, 2003) documented deltamethrin toxicities from agricultural use and accidental or suicidal poisoning. Effects from oral ingestion included epigastric pain nausea, vomiting, coarse muscular fasciculation, and coma. Workers exposed to deltamethrin during its manufacture experienced cutaneous and mucous membrane irritation. These reviews and OEHHA's literature review, however, have not identified children specific data. Thus, the potential effects of deltamethrin are based on animal data.

The developmental neurotoxicity of pyrethroids was recently reviewed, which offers some insight on the potential effects of deltamethrin (Shafer et al. 2005). While the mechanisms of action on the developing brain have not been completely worked out, the review presented some evidence to suggest the vulnerability of children to pyrethroids. Specifically, pyrethroids could disrupt voltage-sensitive sodium channel (VSSC) function and expression during development, leading to irreversible neurotoxic effects. Pyrethroids are known to bind the α-subunit of VSSCs. Different forms of the α-subunit are expressed during neurodevelopment. For example, high expression of $Na_v1.3$ during the embryonic period diminishes as expression of $Na_v1.2$ increases in the early postnatal period. The latter α-subunit is replaced by $Na_v1.6$ as myelination proceeds. The authors concluded that given the previously reported differences in α-subunit sensitivity to pyrethroids, the complex ontogeny of VSSC expression could result in altered sensitivity and perturbation of the developing nervous system by pyrethroids. Phenytoin, an anticonvulsant having a mode of action similar to that of pyrethroids in interfering with the activity of VSSCs, was further used to illustrate the potential effect of pyrethroids. In humans, the use of phenytoin during pregnancy has been associated with a number of defects in offspring including microcephaly and intellectual impairment. Studies in animal models support the human findings. However, the authors were careful to underscore that there are currently no data to suggest that developmental exposure to pyrethroids results in similar effects.

OEHHA also reviewed the literature specific to deltamethrin, including the Eriksson and Ray studies cited by ATSDR. Pertinent studies from the targeted review are summarized in Table 2. Collectively these studies provide a picture that prenatal or early postnatal exposure to deltamethrin, at doses below those that cause overt neurotoxic symptoms, could alter normal brain development and maturation. The effects of deltamethrin could manifest themselves later in life. Thus, infants in daycare centers and young school children would be vulnerable to deltamethrin exposure.

Table 2

Study	Test Species	Exposure Route & Duration	Testing Time & Critical Effects	LOAEL (mg/kg-day)
(Eriksson and Fredriksson, 1991)	NMRI mice	Oral; postnatal day (PND) 10-16	At PND 17, no significant behavioral effects. At 4 months old, significant increase in locomotion & total activity and significant decrease in cholinergic receptors in cerebral cortex.	0.7
(Aziz et al. 2001)	Albino Wistar rats	Oral; gestational days (GD) 14-20	Significant increase in cholinesterase activity and decrease in cholinergic receptors in hippocampus, and decrease in learning and memory performance observed at both 6 and 12 weeks old,	1.0
(Patro et al. 1997)	Wistar rats	Intraperitoneal injection; PND 9-13	Histopathology at PND 12, 15, 21 or 30. Observed delay in cytogenesis and morphogenesis of neurons in cerebellum, and damage of developing vasculature.	0.7
(Husain et al. 1994)	Albino Wistar rats	Oral; PND 22-37	At PND 38 observed significant decrease in hippocampus weight, increase in cholinesterase, decrease in cholinergic	7.0

			receptors, impaired learning function and increased locomotion.	
(Lazarini et al. 2001)	Wistar rats	Oral, GD 6-15	At PND 60, a anxiogenic swimming procedure followed by open-field behavior testing indicated treated male rats having a significantly increased in emotional state.	0.08

In the Aziz et al. (2001) study, deltamethrin (grade not reported) at a dose of 1 mg/kg-day was orally given to pregnant albino Wistar rats from GD 14-20. No gross abnormality was observed in deltamethrin exposed or unexposed rats. Body weights of treated and control pups were not significantly different. Acetylcholinesterase (AchE) in the hippocampal region was increased by 28 and 16 percent ($P<0.05$) in exposed progeny at 6 and 12 weeks of age, respectively. MACh receptors, on the other hand, were significantly reduced in the hippocampus when measured at those same time periods. A significant decrease in relearning performance (memory) of the exposed progeny was also noted when they were subjected to a Y maze test at 6 and 12 weeks.

Patro et al. (1997) exposed young Wistar rats to 0.7 mg/kg-day of deltamethrin (grade not specified) by Intraperitoneal injection between PND 9-13. The animals were weighted and histopathology was performed on the cerebellum at PND 12, 15, 21, and 30. The body and brain weights of the treated rats were significantly lower than the controls. The authors observed a delay in cytogenesis and morphogenesis of neurons in the cerebellum. Damage to the developing vasculature, and focal degeneration and spongy appearance of the tissues in the vicinity of the damaged blood vessels were also noted.

Husain et al. (1994) administered deltamethrin formulation orally to 50 albino Wistar male rats from PND 22-37 at a dose of 7 mg/kg-day. Various assays and behavioral testing were performed on PND 38. There were no significant differences in body and whole brain weights of treated and untreated rats, except for a significant decrease in the wet weight of the hippocampus. A significant elevation of the activity of monoamine oxidase and AchE , a slight but significant increase in spontaneous locomotor activity, and impaired, learning performance, were observed in treated rats. A significant enhancement in dopaminergic and lowering of MACh receptors in the corpus striatum were noted in comparison to controls.

In the Lazarini et al. (2001) study, deltamethrin formulation was orally administered to nine pregnant Wistar rats from GD 6-15 at a dose of 0.08 mg/kg-day. Prenatal exposure did not affect maternal and offspring body weight. At PND 60, rats were subject to a swimming test and open-field behaviors were measured 15 minutes after the swimming test. The swimming test, in which rats were plunged individually into a vertical glass

cylinder to induce anxiety, was used as a challenge to detect possible subtle effects of low-dose deltamethrin during open-field testing. Treated male rats showed significantly decreased peripheral, median and central locomotion frequencies, as well as significantly increased immobility duration. At PND 140, animals were sacrificed and striatal monoamine levels were measured. Treated males exhibited a significantly higher striatal DOPAC (3,4-dihydroxyphenylacetic acid, a dopamine metabolite) levels and DOPAC/dopamine ratio. However, the authors expressed the concern that the deltamethrin formulation used may have included xylene as a solvent, which could potentially enhance the effects of deltamethrin.

In summary, there is some concern that lower body weight gain in the treatment group may confound the observed results in the Patro study. Studies, which used a deltamethrin formulation or did not report the grade of deltamethrin, also present some challenge in terms of interpreting the dose and response. However, the use of formulations may provide a more realistic exposure scenario. These studies from Sweden, India and Brazil help paint an overall picture of the effects of deltamethrin or its formulation on the developing brain.

The Ray study, in which the authors concluded that they could not replicate the results of Eriksson's study on deltamethrin, was published as an abstract (Ray et al. 2002) and as a letter to the editor (Muhammad et al. 2003), rather than as a full article in a peer review journal. Aside from not having the benefit of peer review, the brevity of the information rendered does not permit one to follow the experimental set up and discern how the receptor binding and behavioral studies were conducted. The authors also acknowledged that they did not follow Eriksson's original experimental conditions in its entirety. In particular, the male and female mice were not separately housed, as done in the original study. This condition may influence the outcome of these behavioral studies. In comparing habituation data between the two studies, Ray et al. noted that the rate of habituation in their controls was markedly slower. This reduced their ability to detect any delay in habituation in the treatment group (habituation is defined by a decrease in locomotion, rearing, and/or total activity in response to the diminished novelty of the test chambers (Eriksson and Fredriksson, 1991)).

Which study should be used as a basis for establishing the child-specific reference dose for deltamethrin?

While collectively the studies in Table 2 provide suggestive evidence on the developmental neurotoxicity of deltamethrin, OEHHA shares the views of Shafer et al. (2005) that there are limitations to these studies. Thus, OEHHA decides not to use any of the studies in Table 2 as the critical study for developing the chRD for deltamethrin. Table 3 summarizes those studies used by CDPR and U.S. EPA for establishing margins of exposure and tolerance levels, respectively.

Table 3

Study	Use	LOAEL* or NOAEL** (mg/kg-day)	Test Species	Exposure Route and Duration	Endpoint
Goldenthal	For CDPR to calculate chronic margin of exposure	0.1 **	Rat	Oral, two years	Degeneration of sciatic, tibial, and plantar nerves
Chesterman	For CDPR to calculate acute/subchronic margin of exposure	0.1 *	Dog	Oral, 13 weeks	Neural--liquid feces, vomiting, and tremors
Ryle	For U.S. EPA to establish tolerance levels	1.0 **	Dog	Oral, 52 weeks	Neural--chewing and scratching of extremities, and liquid feces

In evaluating these studies, OEHHA opts to use the 1980 Goldenthal study as a basis for developing the chRD. Unlike the Chesterman study, solvent, which may enhance the toxicity of deltamethrin, was not used. The Goldenthal study also provides a lower NOAEL compared to the Ryle study used by U.S. EPA in setting tolerance levels.

OEHHA agrees with U.S. EPA that a 3X factor should be applied to account for age-related sensitivity (brain concentration of deltamethrin in weanling rats was higher than in adult rats (Sheets et al., 1994)); however, OEHHA disagrees with U.S. EPA that a database deficiency factor is not needed. There is suggestive evidence that deltamethrin adversely impacts the developing brain. Additional developmental neurotoxicity studies, which include functional tests and span the dose range below 1.0 mg/kg-day, should be conducted to adequately quantify the impact. In the interim, a database deficiency factor should be applied. The lowest LOAEL observed from the non-guideline developmental neurotoxicity studies is 0.08 mg/kg-day, which yields an estimated NOAEL of 0.008 mg/kg-day. In comparing this estimated NOAEL to the chronic NOAEL of 0.1 mg/kg-day (proposed for use in developing the chRD), an inference can be drawn that children could potentially be 12.5 times more sensitive to deltamethrin. A factor of three will be applied to account for pharmacokinetics (brain concentration difference). OEHHA proposes to apply another factor of 3 due to deficiencies in the developmental

neurotoxicity database. Combining these two factors of three results in a safety factor of 10 to address the overall 12.5 fold increase in children sensitivity.

The calculation of the chRD for deltamethrin is given below:

$$chRD = \frac{NOAEL}{UF} = \frac{0.1\,\text{mg/kg - day}}{1000} = 0.0001 mg/kg - day$$

Where,

UF = Uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for human variability, and 10 from combining a factor of three for neurotoxicity database deficiency and a factor of three for age-difference in brain concentration).

DRAFT

References

ARB and DHS (2003) California Portable Classroom Study, Phase 2 Final Report Volume II, prepared for the California Air Resources Board and California Department of Health Services, by RTI International.

ATSDR (2001) Draft Toxicological Profile for Pyrethrins and Pyrethroids.

ATSDR (2003) Toxicological Profile for Pyrethrins and Pyrethroids.

Aziz, M.H., Agrawal, A.K., Adhami, V.M., Shukla, Y. and Seth, P.K. (2001) Neurodevelopmental consequences of gestational exposure (GD14-GD20) to low dose deltamethrin in rats. *Neurosci Lett; 300(3):161-5.*

CDPR (California Department of Pesticide Regulation) (2000) Deltamethrin: Risk Characterization Document.

Chesterman, H. (1977) RU 22974 Oral Toxicity Study in Beagle Dogs. Huntingdon Research Centre Study submitted with application for registration of deltamethrin technical, AgrEvo Environmental Health, Inc., Roject Number RSL 253/77251, DPR Document 51846-007 #129661

Eriksson, P. and Fredriksson, A. (1991) Neurotoxic effects of two different pyrethroids, bioallethrin and deltamethrin, on immature and adult mice: changes in behavioral and muscarinic receptor variables. *Toxicol Appl Pharmacol; 108(1):78-85.*

Goldenthal, E. (1980) Two-year Oral Toxicity and Carcinogenicity Study in Rats. International Research and Development study submitted with application for registration of deltamethrin technical, AgrEvo Environmental health, Inc., Project Number 406-022/A4, DPR Document 51846-022 #132785

Husain, R., Malaviya, M., Seth, P.K. and Husain, R. (1994) Effect of deltamethrin on regional brain polyamines and behaviour in young rats. *Pharmacol Toxicol 1994 Apr-May;74(4-5):211-5.* **74**, 211-5.

Lazarini, C.A., Florio, J.C., Lemonica, I.P. and Bernardi, M.M. (2001) Effects of prenatal exposure to deltamethrin on forced swimming behavior, motor activity, and striatal dopamine levels in male and female rats. *Neurotoxicol Teratol* **23**, 665-73.

Muhammad, B.Y., Verschoyle, R.D. and Ray, D.D. (2003) Developmental toxicity of pyrethroids. *Arch Toxicol* **77**, 48-9.

Patro, N., Mishra, S.K., Chattopadhyay, M. and Patro, I.K. (1997) Neurotoxicological effects of deltamethrin on the postnatal development of cerebellum of rat. *Journal of Bioscience* **22** , 117-130.

Ray, D.E., Verschoyle, R.D. and Muhammad B. Y. (2002) Reproducibility of developmental neurotoxicity produced by pyrethroids and DDT in neonatal mice. *Toxicologist* **66(1-S)**, 131.

Ryle, P. et al. (1993) Deltamethrin (Technical) Toxicity to Dogs by Repeated Daily Administration for 52 Weeks. Huntingdon Research Centre study submitted for registration of deltamethrin technical, AgrEvo Environmental Health, Inc.

Shafer, T.J., Meyer, D.A. and Crofton, K.M. (2005) Developmental Neurotoxicity of Pyrethroid Insecticides: Critical Review and Future Research Needs. *Environmental Health Perspectives* **113**, 123-136.

Sheets, L., Doherty, J., Law, M., Reiter, L., and Crofton, K. (1994) Age-Dependent Differences in the Susceptibility of Rats to Deltamethrin. *Toxicology and Applied Pharmacology* **126**, 186-190.

U.S. EPA (2004) Deltamethrin: Pesticide Tolerance Final Rule. *Federal Register* **69** (207), 62602-62615.